BMC Nephrology

RESEARCH

Open Access

Associations between inflammatory markers and carotid plaques in CKD: mediating effects of eGFR–a cross-sectional study

Li Wang[1,2,3†], Jialin Wang[1,2,3†], Jun Ji[1,2,3], Fangfang Xiang[1,2,3], Lin Zhang[1,2,3], Xiaotian Jiang[1,2,3], Yi Fang[1,2,3], Xiaoqiang Ding[1,2,3*] and Wuhua Jiang[1,2,3*]

Abstract

Background Chronic kidney disease (CKD) is a significant public health concern associated with a high prevalence of carotid plaques, which are indicators of atherosclerosis and predictors of adverse cardiovascular outcomes. Inflammation is a hallmark of CKD, contributing to both renal dysfunction and cardiovascular complications. This study aims to investigate the association between inflammatory markers—systemic inflammatory response index (SIRI), systemic immune-inflammation index (SII), aggregate inflammatory status index (AISI), monocyte to high-density lipoprotein cholesterol ratio (MHR), neutrophil to high-density lipoprotein cholesterol ratio (NHR), neutrophil to lymphocyte ratio (NLR), and monocyte to lymphocyte ratio (MLR)—and carotid plaques in CKD patients, and to explore the potential mediating role of estimated glomerular filtration rate (eGFR) in this relationship.

Methods A cross-sectional analysis was conducted on patients admitted to the Division of Nephrology between January 2023 and June 2023. The primary endpoint was the presence of carotid plaques assessed using ultrasound imaging. Multivariable logistic regression models were used to examine the associations between inflammatory markers and carotid plaques, and trend tests were performed to evaluate the trending association of carotid plaques risk and inflammatory markers in tertiles. Restricted cubic spline (RCS) analysis was used to assess potential non-linear relationships, and subgroup analyses were conducted to examine consistency across different strata. Mediation analysis was performed to explore the role of eGFR.

Results Of the 609 participants, 387 were included in the final analysis after applying exclusion criteria. Elevated levels of LnSIRI (OR = 1.87, 95% CI = 1.25–2.80), LnSII (OR = 1.67, 95% CI = 1.09–2.56), LnAISI (OR = 1.70, 95% CI = 1.22–2.37), LnMHR (OR = 1.94, 95% CI = 1.15–3.26), LnNHR (OR = 1.82, 95% CI = 1.10–3.02), and LnMLR (OR = 2.26, 95% CI = 1.18–4.34) were significantly associated with the presence of carotid plaques. There were significant trends for increasing tertiles of SIRI, AISI, MHR and NHR. RCS analysis showed no significant non-linear associations. Subgroup

†Li Wang and Jialin Wang contributed equally to this work.

*Correspondence:
Xiaoqiang Ding
ding.xiaoqiang@zs-hospital.sh.cn
Wuhua Jiang
jiangwuhua@msn.cn

Full list of author information is available at the end of the article

analyses indicated similar associations across most strata. eGFR partially mediated these relationships, with proportions mediated ranging from 14.7 to 17.5%.

Conclusions Inflammatory markers are significantly associated with carotid plaques in CKD patients, with eGFR playing a partial mediating role. These findings highlighted the importance of managing inflammation and maintaining renal function to mitigate the risk of atherosclerosis in CKD patients.

Trial registration Not applicable.

Keywords Chronic kidney disease, Inflammatory markers, Carotid plaque, Estimated glomerular filtration rate, Atherosclerosis

Introduction

Chronic kidney disease (CKD) is a significant public health concern, affecting a substantial proportion of the global population [1]. Among patients with CKD, the prevalence of carotid plaques is notably high [2]. Carotid plaques, which indicate the presence of atherosclerosis, are associated with an increased risk of cardiovascular events, including stroke and myocardial infarction [3]. Epidemiological studies have demonstrated that the presence of carotid plaques in CKD patients is a strong predictor of adverse cardiovascular outcomes and mortality [4, 5]. The increased burden of atherosclerosis in this population underscores the need for early detection and intervention strategies to mitigate the associated risks.

Inflammation is a hallmark of CKD, contributing to the progression of renal dysfunction and the high prevalence of cardiovascular diseases in this population [6, 7]. Various inflammatory markers, including the systemic inflammatory response index (SIRI) [8], systemic immune-inflammation index (SII) [9], and others, are elevated in CKD patients. These markers reflect the underlying inflammatory state and have been implicated in the pathogenesis of atherosclerosis. Inflammation accelerates the development of carotid plaques by promoting endothelial dysfunction, oxidative stress, and vascular calcification [10, 11]. The interplay between inflammation and atherosclerosis in CKD patients highlights the importance of understanding the role of inflammatory markers in the development and progression of carotid plaques.

Given the high prevalence of inflammation and carotid plaques in CKD patients, we hypothesize that elevated levels of inflammatory markers are associated with an increased risk of carotid plaque formation. Furthermore, we propose that the estimated glomerular filtration rate (eGFR) mediates this relationship, as renal dysfunction exacerbates inflammation and its vascular consequences [12]. The primary objective of this study is to investigate the association between inflammatory marker levels and carotid plaques in CKD patients, and to explore the potential mediating role of eGFR in this association. By elucidating these relationships, our study aims to contribute to a better understanding of the mechanisms underlying cardiovascular risk in CKD patients and to identify potential targets for therapeutic intervention.

Methods

Design and study population

This study was a retrospective cross-sectional analysis conducted to explore the associations between inflammatory markers and carotid plaque in patients with CKD. CKD was defined and staged according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines [13]. The study population comprised patients admitted to the Division of Nephrology between January 2023 and June 2023. Ethical approval was obtained from the Zhongshan Hospital Ethics Committee (B2021-740), and all eligible participants provided written informed consent.

Exclusion criteria

(1) Patients undergoing renal replacement therapy. (2) Recent use of antibiotics within the past three months. (3) Recent use of drugs known to influence lipid metabolism within the past three months. (4) Recent use of glucocorticoids or immunosuppressants within the past three months. (5) History of New York Heart Association class III/IV heart failure. (6) Presence of acute infection. (7) Diagnosis of liver cirrhosis. (8) Severely elevated serum alanine aminotransferase or aspartate aminotransferase levels (1.5 times higher than the normal upper limit). (9) Diagnosis of malignant tumor. (10) Infection with human immunodeficiency virus. (11) Recent major surgery or trauma within the past three months. (12) Severe anemia (hemoglobin levels below 60 g/dL). (13) Severe electrolyte imbalance. (14) Uncontrolled hypertension (blood pressure consistently above 150/100 mmHg). (15) Active autoimmune diseases (e.g., systemic lupus erythematosus, rheumatoid arthritis). (16) Chronic inflammatory diseases (e.g., Crohn's disease, ulcerative colitis) (17) Recent substance abuse (drugs or alcohol). (18) Recent vaccination (past one month) (19) Severe obesity (BMI > 40 kg/m^2). (20) Pregnancy. (21) Missing ultrasound of carotid artery.

Definitions

Inflammatory markers

Inflammatory markers were calculated using blood sample data. Blood specimens were collected in the morning after at least nine hours of overnight fasting. Full blood counts were obtained from BD EDTA-K2 samples and analyzed using a Sysmex XN9000 electronic counter. To measure HDL-C levels, Chemistry Analyzer Roche Cobas c702 and Roche modular P were utilized. The formulas for the inflammatory markers are as follows:

(1) Systemic Inflammatory Response Index (SIRI): Calculated as neutrophil count (10^9/L) times monocyte count (10^9/L) divided by lymphocyte count (10^9/L).
(2) Systemic Immune-Inflammation Index (SII): Calculated as platelet count (10^9/L) times neutrophil count (10^9/L) divided by lymphocyte count (10^9/L).
(3) Aggregate Inflammatory Status Index (AISI): Calculated as neutrophil count (10^9/L) times monocyte count (10^9/L) times platelet count (10^9/L) divided by lymphocyte count (10^9/L).
(4) Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR): Calculated as monocyte count (10^9/L) divided by HDL-C (mg/dL).
(5) Neutrophil to High-Density Lipoprotein Cholesterol Ratio (NHR): Calculated as neutrophil count (10^9/L) divided by HDL-C (mg/dL).
(6) Neutrophil to Lymphocyte Ratio (NLR): Calculated as neutrophil count (10^9/L) divided by lymphocyte count (10^9/L).
(7) Monocyte to Lymphocyte Ratio (MLR): Calculated as monocyte count (10^9/L) divided by lymphocyte count (10^9/L).

Body Mass Index (BMI)

BMI was calculated as weight in kilograms divided by height in meters squared (kg/m²).

Estimated glomerular filtration rate (eGFR)

eGFR was calculated using the CKD-EPI formula [14].

Carotid plaque

Carotid plaque was assessed using ultrasound imaging and defined as a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding intima-media thickness (IMT) value or demonstrates a thickness of more than 1.5 mm as measured from the intima-lumen interface to the media-adventitia interface [15].

Covariates

Covariates included age, sex, body mass index, eGFR, smoking status, diabetes mellitus, hypertension, cardiovascular and cerebrovascular diseases (CCVD), hemoglobin, and serum albumin. These covariates were selected based on their potential confounding effects on the relationship between inflammatory markers and carotid plaque.

Statistical analysis

Descriptive statistics

Data following a normal distribution were presented as mean±standard deviation, while those not normally distributed were shown as medians with interquartile ranges. Categorical data were expressed as frequencies and percentages. Differences between groups (carotid plaque vs. no carotid plaque) were assessed using the Student's t-test or the Wilcoxon rank sum test for continuous variables and the Pearson's chi-squared test for categorical variables.

Multivariable logistic regression

Due to the non-normal distribution of inflammatory markers, natural logarithm (Ln) transformations were applied. Multivariable logistic regression models were used to examine the associations between ln-transformed inflammatory markers and the presence of carotid plaque. Three models were constructed:

Model 1 Crude analysis.

Model 2 Adjusted for age, sex, and BMI.

Model 3 Adjusted for age, sex, BMI, eGFR, smoking status, diabetes mellitus, hypertension, CCVD, hemoglobin, and serum albumin.

The results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). Additionally, each marker was categorized into tertiles to examine trends across increasing levels.

Mediation analysis

Mediation analysis was performed to explore the potential mediating effect of eGFR on the relationship between inflammatory markers and carotid plaque. The total, direct, and indirect effects were calculated, and the proportion mediated was reported with 95% CIs.

Subgroup and non-linear analyses

Subgroup analyses were conducted to investigate the consistency of the associations across various strata, including age, sex, BMI, eGFR, smoking status, diabetes mellitus, and hypertension. Restricted cubic spline (RCS) analyses were used to assess potential non-linear

relationships between ln-transformed inflammatory markers and carotid plaque.

Statistical Software

All statistical analyses were performed using R software (version 4.3.2). Descriptive statistics and logistic regression analyses were conducted using the base and stats packages in R. Mediation analyses were performed using the mediation package. Restricted cubic spline analyses were conducted using the rms package. A two-sided P value of <0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 609 patients were initially screened for this study, and after applying the exclusion criteria, 387 patients were included in the analysis (Fig. 1), among which 130 were with carotid plaque. The baseline characteristics of the study participants are presented in Table 1. The median age of participants with carotid plaque was significantly higher than those without (63 years [IQR: 56–72] vs. 48 years [IQR: 36–58], $P<0.001$). The proportion of males was higher in the carotid plaque group compared to the non-plaque group (70.0% vs. 56.0%, $P=0.008$). Participants with carotid plaque had a higher prevalence of diabetes mellitus (44.6% vs. 17.5%, $P<0.001$), hypertension (85.4% vs. 66.1%, $P<0.001$), and CCVD (28.5% vs. 7.4%, $P<0.001$). In terms of laboratory indices, participants with carotid plaque had significantly higher median levels of blood urea nitrogen (BUN) and serum creatinine (SCr), but lower levels of hemoglobin and eGFR. Inflammatory markers, such as SIRI, SII, AISI,

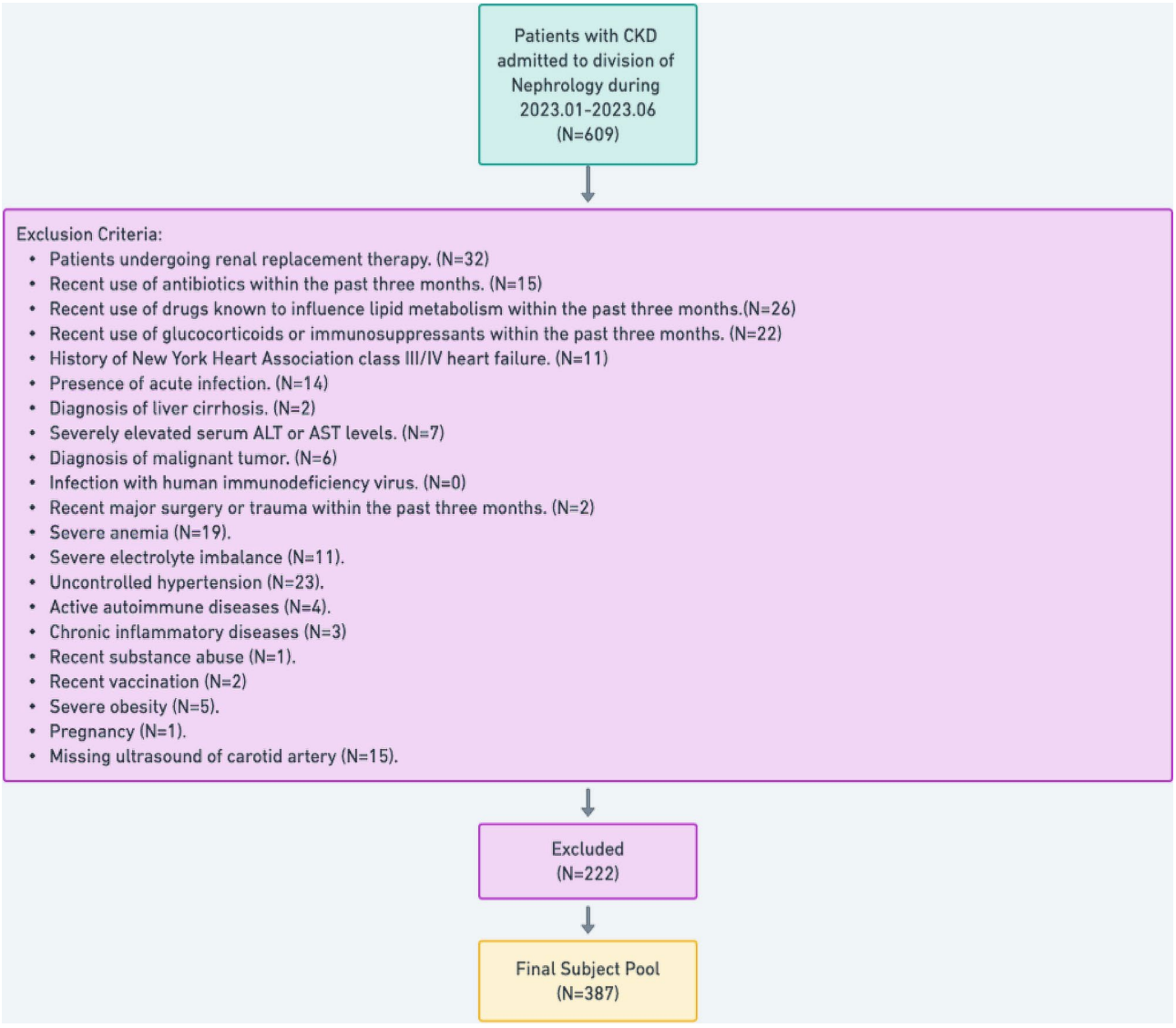


Fig. 1 Flowchart of the patients enrollment

Table 1 Patient demographics and baseline characteristics

Characteristic	Carotid Plaque		*P*
	No, $N=257$[1]	Yes, $N=130$[1]	
Demographics			
Age (y)	48 (36, 58)	63 (56, 72)	< 0.001
Male (%)	144 (56.0%)	91 (70.0%)	0.008
BMI (kg/m^2)	23.7 (21.7, 26.4)	24.7 (22.4, 26.8)	0.122
Smoking (%)	36 (14.0%)	28 (21.5%)	0.060
Diabetes Mellitus (%)	45 (17.5%)	58 (44.6%)	< 0.001
Hypertension (%)	170 (66.1%)	111 (85.4%)	< 0.001
CCVD (%)	19 (7.4%)	37 (28.5%)	< 0.001
Laboratory indices			
Hemoglobin (g/L)	122 (98, 137)	111 (93, 128)	0.016
Serum albumin (g/L)	36 (31, 39)	35 (31, 38)	0.086
BUN (mmol/L)	7 (5, 17)	11 (7, 18)	0.001
SCr (umol/L)	119 (78, 333)	154 (107, 355)	0.056
UA (umol/L)	410 (345, 504)	433 (359, 510)	0.221
eGFR (mL/min/1.73m^2)	57 (16, 92)	37 (14, 64)	0.005
Proteinuria (g/24 h)	1.79 (0.89, 3.56)	2.37 (0.95, 4.06)	0.113
TC (mmol/L)	4.77 (4.15, 5.65)	4.76 (3.90, 5.92)	0.993
TG (mmol/L)	1.72 (1.29, 2.47)	1.73 (1.17, 2.42)	0.738
HDL (mmol/L)	1.08 (0.89, 1.39)	1.11 (0.87, 1.40)	0.742
LDL (mmol/L)	2.72 (2.20, 3.51)	2.79 (2.16, 3.60)	0.901
WBC ($\times 10^9$/L)	6.37 (5.16, 7.59)	6.65 (5.33, 8.02)	0.117
Neutrophil ($\times 10^9$/L)	3.90 (3.00, 4.80)	4.10 (3.20, 5.48)	0.101
Lymphocyte ($\times 10^9$/L)	1.70 (1.30, 2.20)	1.65 (1.20, 2.18)	0.184
Monocyte ($\times 10^9$/L)	0.37 (0.28, 0.49)	0.42 (0.34, 0.53)	< 0.001
CRP (mg/L)	1.2 (0.6, 2.5)	2.0 (1.0, 4.9)	< 0.001
Inflammatory markers			
SIRI ($\times 10^9$/L)	0.83 (0.55, 1.26)	1.03 (0.69, 1.63)	< 0.001
SII ($\times 10^9$/L)	416 (294, 583)	471 (336, 751)	0.037
AISI ($\times 10^9$/L)	149 (97, 248)	193 (126, 336)	0.001
MHR ($\times 10^9$/L/mmol/L)	0.008 (0.006, 0.012)	0.010 (0.007, 0.014)	0.003
NHR ($\times 10^9$/L/mmol/L)	0.09 (0.07, 0.13)	0.10 (0.07, 0.14)	0.098
NLR	2.19 (1.67, 3.00)	2.52 (1.70, 3.56)	0.041
MLR	0.21 (0.17, 0.28)	0.25 (0.19, 0.35)	< 0.001

AISI: aggregate inflammatory status index; BMI: body mass index; BUN: blood urea nitrogen; CCVD: cardiovascular and cerebrovascular diseases; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; HDL: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; MHR: monocyte to high-density lipoprotein cholesterol ratio; MLR: monocyte to lymphocyte ratio; NHR: neutrophil to high-density lipoprotein cholesterol ratio; NLR: neutrophil to lymphocyte ratio; SCr: serum creatinine; SII: systemic immune-inflammation index; SIRI: systemic inflammatory response index; TC: total cholesterol; TG: triglyceride; UA: uric acid; WBC: white blood cell count

MHR, NLR, and MLR, were all significantly elevated in participants with carotid plaque compared to those without.

Association between inflammatory markers and eGFR

A correlation analysis was performed between eGFR and various inflammatory markers (Additional Table 1). The results revealed significant negative correlations between eGFR and multiple inflammatory markers. Specifically, LnSIRI (r = -0.186, $p<0.001$), LnSII (r = -0.118, $p=0.02$), LnMHR (r = -0.144, $p=0.005$), LnNHR (r = -0.224, $p<0.001$), LnNLR (r = -0.293, $p<0.001$), and LnMLR (r = -0.252, $p<0.001$) all showed significant negative correlations with eGFR, indicating that as renal function worsens, systemic inflammation increases. However, LnAISI did not show a significant correlation with eGFR (r = -0.059, $p=0.247$).

Association of inflammatory markers with carotid plaque

After adjusting covariates, Logistic regression suggested an increase in the LnSIRI (OR=1.87, 95%CI=1.25–2.80), LnSII (OR=1.67, 95%CI=1.09–2.56), LnAISI (OR=1.70, 95% CI=1.22–2.37), LnMHR (OR=1.94, 95% CI=1.15–3.26), LnNHR (OR=1.82, 95% CI=1.10–3.02) and LnMLR (OR=2.26, 95% CI=1.18–4.34) were associated with a higher prevalence odds of carotid plaque (Table 2). Compared to the first quartile of SIRI, AISI, MHR, NHR, each increase in a quartile of these inflammatory

Table 2 Adjusted ORs (95% CIs) for carotid plaque according to categorical or continuous inflammatory biomarkers

Variables	Model1		Model2		Model3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
LnSIRI	1.76 (1.30–2.38)	< 0.001	1.84 (1.26–2.69)	0.002	1.87 (1.25–2.80)	0.002
SIRI tertiles						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.47 (0.85–2.52)	0.166	1.14 (0.60–2.18)	0.692	1.12 (0.57–2.22)	0.743
3	2.26 (1.33–3.85)	0.003	2.24 (1.19–4.22)	0.012	2.30 (1.17–4.51)	0.015
P for trend		0.003		0.007		0.007
LnSII	1.47 (1.05–2.06)	0.025	1.72 (1.14–2.59)	0.009	1.67 (1.09–2.56)	0.020
SII tertiles						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.12 (0.66–1.89)	0.679	1.26 (0.67–2.39)	0.472	1.37 (0.71–2.66)	0.348
3	1.52 (0.90–2.55)	0.115	1.83 (0.99–3.39)	0.055	1.77 (0.92–3.40)	0.085
P for trend		0.100		0.052		0.095
LnAISI	1.55 (1.20–2.00)	< 0.001	1.71 (1.24–2.35)	< 0.001	1.70 (1.22–2.37)	0.002
AISI tertiles						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.89 (1.10–3.25)	0.021	1.61 (0.85–3.05)	0.144	1.51 (0.78–2.93)	0.226
3	2.24 (1.30–3.84)	0.004	2.27 (1.20–4.27)	0.011	2.32 (1.20–4.49)	0.013
P for trend		0.009		0.016		0.014
LnMHR	1.75 (1.20–2.54)	0.004	1.76 (1.08–2.89)	0.024	1.94 (1.15–3.26)	0.013
MHR tertiles						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.52 (0.88–2.60)	0.130	1.30 (0.68–2.50)	0.432	1.36 (0.69–2.67)	0.378
3	2.19 (1.29–3.73)	0.004	2.23 (1.12–4.46)	0.023	2.49 (1.21–5.12)	0.013
P for trend		0.004		0.019		0.011
LnNHR	1.39 (0.96–2.03)	0.085	1.76 (1.09–2.82)	0.020	1.82 (1.10–3.02)	0.020
NHR tertiles						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.16 (0.68–1.97)	0.582	1.14 (0.60–2.18)	0.683	1.11 (0.57–2.15)	0.763
3	1.63 (0.97–2.74)	0.066	2.20 (1.14–4.25)	0.019	2.23 (1.10–4.53)	0.026
P for trend		0.058		0.012		0.019
LnNLR	1.56 (1.06–2.30)	0.025	1.63 (1.02–2.60)	0.041	1.62 (0.97–2.71)	0.063
NLR tertiles						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.08 (0.63–1.84)	0.791	0.96 (0.51–1.81)	0.895	1.16 (0.60–2.25)	0.660
3	1.82 (1.08–3.07)	0.024	1.84 (0.98–3.46)	0.058	2.00 (0.99–4.03)	0.052
P for trend		0.014		0.030		0.039
LnMLR	2.83 (1.72–4.64)	< 0.001	2.04 (1.13–3.69)	0.018	2.26 (1.18–4.34)	0.014
MLR tertiles						
1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
2	1.58 (0.91–2.74)	0.102	1.01 (0.53–1.92)	0.983	1.01 (0.51–2.00)	0.977
3	2.46 (1.44–4.21)	< 0.001	1.53 (0.82–2.86)	0.182	1.61 (0.82–3.16)	0.164
P for trend		< 0.001		0.139		0.119

Model1: Crude

Model2: Adjust: sex, age, BMI

Model3: Adjust: sex, age, BMI, eGFR, smoking, diabetes mellitus, hypertension, cardiovascular and cerebrovascular diseases, hemoglobin, serum albumin

AISI: aggregate inflammatory status index; BMI: body mass index; CI: confidence interval; eGFR: estimated glomerular filtration rate; Ln: natural logarithm; MHR: monocyte to high-density lipoprotein cholesterol ratio; MLR: monocyte to lymphocyte ratio; NHR: neutrophil to high-density lipoprotein cholesterol ratio; NLR: neutrophil to lymphocyte ratio; OR: odds ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammatory response index

markers were significantly associated with an increased OR for carotid plaque, and there is a significant trend (*P*-trend < 0.05, Table 2). Figure 2 reveals no nonlinear association of inflammatory markers with carotid plaque through restricted cubic spline analysis.

Subgroup analysis

In the subgroup analysis based on the natural logarithm-transformed levels of inflammatory markers (Fig. 3), the associations between the markers and carotid plaque were similar across most strata (P for interaction > 0.05). A significant interaction was observed only for MLR and carotid plaque in the context of hypertension ($P=0.018$).

We further observed that inflammatory markers, including SIRI, SII, MHR, NLR, and MLR, were significantly associated with carotid plaque formation in patients with eGFR < 15 mL/min/1.73 m^2, while NHR did not show a significant association in this group (Fig. 3).

The mediating roles of eGFR in the relationship between inflammatory markers and carotid plaque

Table 3 presents the mediating effect of eGFR on the association between inflammatory markers and carotid plaque risk. This study revealed significant indirect effects of inflammatory markers (LnSIRI, LnSII, LnMHR, LnMLR) on carotid plaque risk through eGFR (*P* values < 0.05). The proportions mediated by eGFR for the inflammatory-associated carotid plaque were 14.8%, 17.5%, 15.1%, and 14.7%, respectively.

Discussion

This study aimed to elucidate the relationship between inflammatory markers and carotid plaques in patients with CKD, and to explore the potential mediating role of eGFR. Our findings indicated that elevated levels of inflammatory markers such as the SIRI, SII, AISI, MHR, NHR, and MLR are significantly associated with the presence of carotid plaques in CKD patients. The association was consistent among various subgroups. Our subgroup analysis further highlighted that in patients with severe renal dysfunction (eGFR < 15 mL/min/1.73 m^2), most inflammatory markers, including SIRI, SII, MHR, NLR, and MLR, were strongly associated with carotid plaques, suggesting that systemic inflammation may play a more pronounced role in atherosclerosis in advanced CKD stages. Furthermore, eGFR was found to partially mediate the relationship between these inflammatory markers and carotid plaques. These results underscored the critical role of inflammation in the pathogenesis of atherosclerosis in CKD patients and highlighted the importance of renal function in modulating this relationship.

Inflammation plays a pivotal role in the development of atherosclerosis and carotid plaques [16]. Numerous studies have highlighted the association between various inflammatory markers and arterial plaque formation. Higher SII levels have been linked to increased arterial plaque burden. A study [17] demonstrated that SII was independently associated with the presence of carotid plaques in a general population, suggesting its role in atherosclerosis development. Another retrospective case-control study [18] analyzed the relationship between novel inflammatory markers and carotid atherosclerosis in a cohort of 10,015 patients. The study found that higher levels of NLR, neutrophil-to-lymphocyte platelet ratio (NLPR), SII, SIRI, and AISI were significantly associated with carotid atherosclerosis. Among these markers, NLPR demonstrated the highest predictive value for carotid atherosclerosis, suggesting its potential as an effective early warning indicator for carotid atherosclerosis.

The MHR has also been identified as a significant marker for arterial plaque formation. A study [19]demonstrates that the MHR was a significant predictor of carotid intima-media thickness in patients with type 2 diabetes mellitus. MHR was shown to be correlated with both the presence and progression of subclinical carotid atherosclerosis, making it a useful measure for evaluating cardiovascular risk in diabetic patients.

CKD is intrinsically linked with a heightened inflammatory state [7], which plays a pivotal role in the progression of the disease and its associated complications. This persistent inflammation is largely due to the impaired clearance of the cytokines by the damaged kidneys, leading to their accumulation in the bloodstream. Moreover, uremic toxins, which accumulate as kidney function declines, further stimulate the production of inflammatory mediators [20]. The chronic inflammatory state in CKD contributes to atherosclerosis and vascular calcification, significantly increasing the risk of the formation of carotid plaques [21, 22].

We conducted a correlation analysis to explore the relationships between eGFR and various inflammatory markers. Our findings demonstrated significant negative correlations between eGFR and most inflammatory markers, including SIRI, SII, MHR, NHR, NLR, and MLR. This suggests that as renal function deteriorates, systemic inflammation tends to increase, consistent with the role of inflammation in the progression of CKD. The lack of significant correlation between AISI and eGFR may indicate that not all inflammatory markers are equally influenced by renal function, highlighting the complex and multifaceted nature of inflammation in CKD. These results underscore the importance of controlling both inflammation and preserving renal function to mitigate cardiovascular risks in CKD patients.

The partial mediation of the relationship between inflammatory markers and carotid plaques by eGFR highlighted the complex interplay between renal function

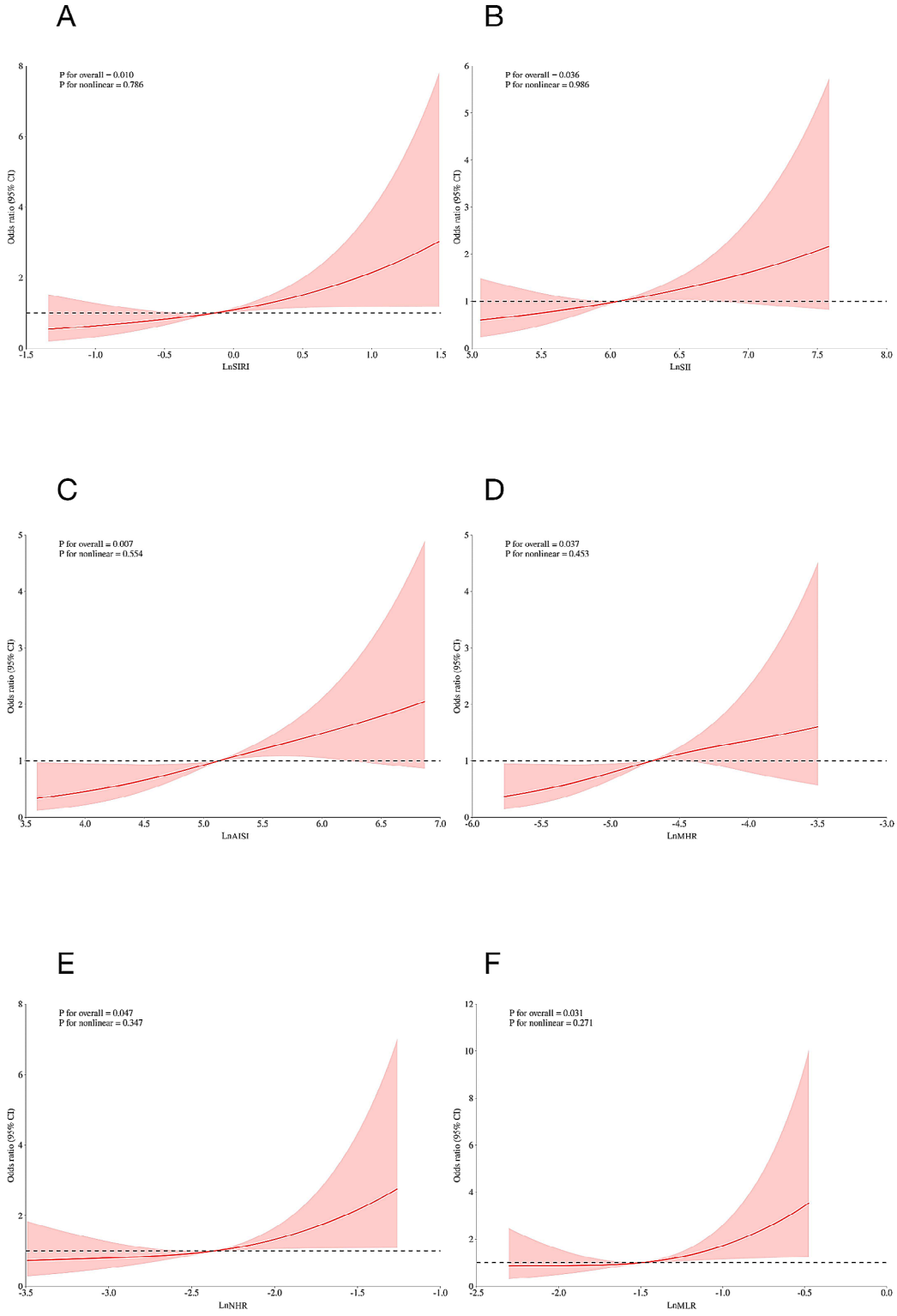
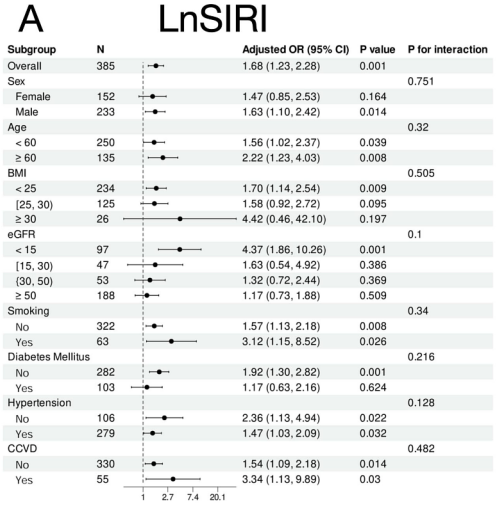
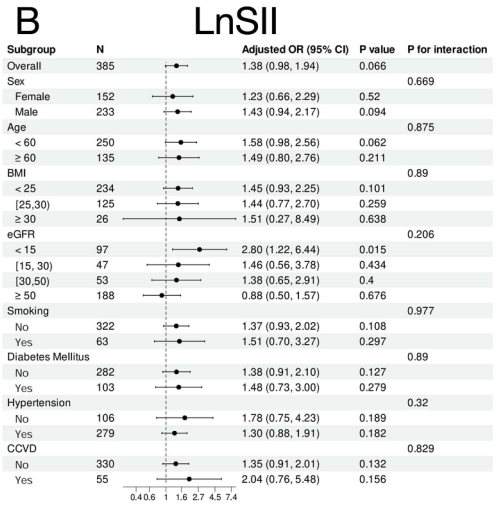
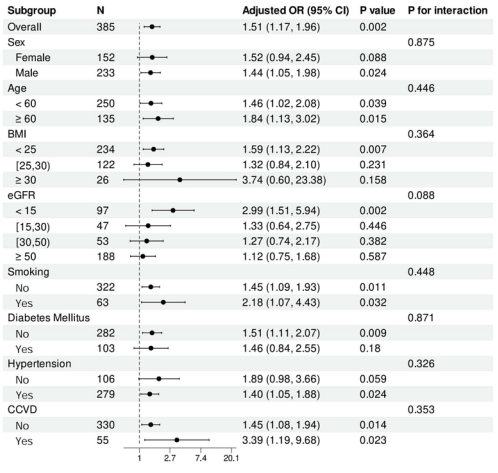
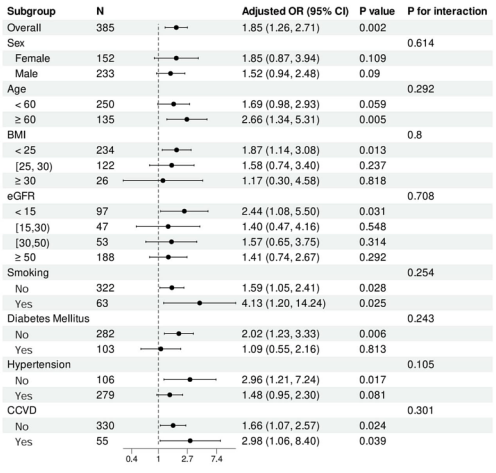


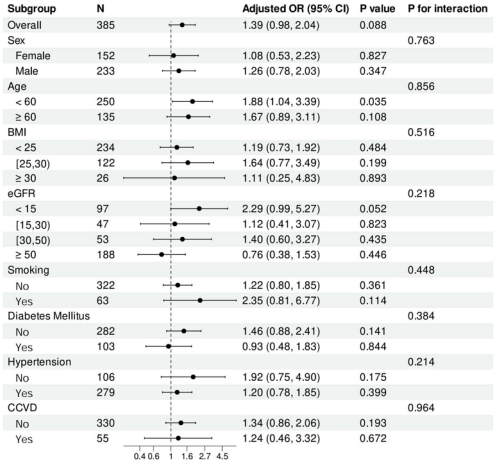
Fig. 2 Restricted cubic spline (RCS) plots showing the non-linear relationship between natural logarithm-transformed inflammatory biomarkers and the odds of carotid plaque in chronic kidney disease (CKD) patients. (**A**) Systemic Inflammatory Response Index (LnSIRI); (**B**) Systemic Immune-Inflammation Index (LnSII); (**C**) Aggregate Inflammatory Status Index (LnAISI); (**D**) Monocyte to High-Density Lipoprotein Cholesterol Ratio (LnMHR); (**E**) Neutrophil to High-Density Lipoprotein Cholesterol Ratio (LnNHR); (**F**) Monocyte to Lymphocyte Ratio (LnMLR). The red lines represent the odds ratios (ORs) for carotid plaque with 95% confidence intervals (CIs) shaded in pink. The dotted horizontal line represents the reference value (OR = 1). P for overall indicates the overall significance of the association, and P for nonlinearity tests whether the relationship deviates from linearity











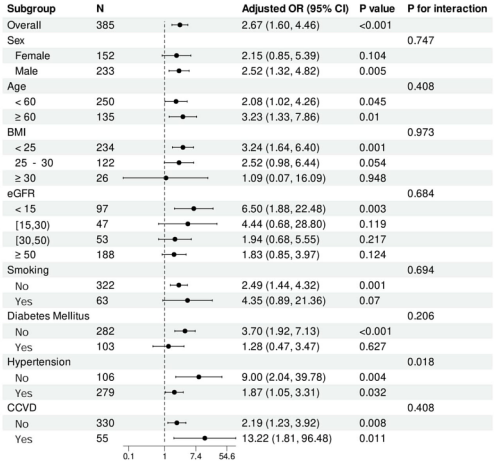


Fig. 3 (See legend on next page.)

(See figure on previous page.)

Fig. 3 Forest plots showing the adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the association between natural logarithm-transformed inflammatory biomarkers and carotid plaque across different subgroups of chronic kidney disease (CKD) patients. (**A**) Systemic Inflammatory Response Index (LnSIRI); (**B**) Systemic Immune-Inflammation Index (LnSII); (**C**) Aggregate Inflammatory Status Index (LnAISI); (**D**) Monocyte to High-Density Lipoprotein Cholesterol Ratio (LnMHR); (**E**) Neutrophil to High-Density Lipoprotein Cholesterol Ratio (LnNHR); (**F**) Monocyte to Lymphocyte Ratio (LnMLR). The subgroups include overall population, sex (female and male), age (< 60 and ≥ 60 years old), body mass index (BMI) categories (< 25, 25–30, and > 30 kg/m^2), estimated glomerular filtration rate (eGFR) categories (< 15, 15–30, 30–50, and > 50 ml/min/1.73m^2), smoking status (smokers and non-smokers), diabetes mellitus (yes and no), hypertension (yes and no), and cardiovascular and cerebrovascular diseases (CCVD) (yes and no). P for interaction values indicate the statistical significance of the interaction between the subgroups and the inflammatory biomarkers

and inflammation in the pathogenesis of atherosclerosis. Reduced eGFR reflected impaired renal clearance, which can lead to an accumulation of inflammatory mediators and exacerbate vascular inflammation and plaque formation [10, 23, 24].

Our findings highlighted a significant association between inflammation and atherosclerosis in CKD patients, with eGFR playing a partial mediating role in this relationship. Clinically, this suggests that managing systemic inflammation and preserving renal function are critical strategies for reducing the risk of atherosclerosis and related cardiovascular events in CKD patients. In the context of hospital care, we recommend a comprehensive approach that includes routine monitoring of inflammatory markers and renal function. Therapeutic interventions should focus on anti-inflammatory strategies and optimization of renal protection, including careful management of blood pressure, proteinuria, and the use of nephroprotective agents. Additionally, early detection of atherosclerotic changes via carotid ultrasound or other modalities could guide timely intervention to prevent further cardiovascular complications.

Study limitations

Despite the significant findings, our study has several limitations that warrant consideration. First, the cross-sectional design precludes the establishment of causality between inflammatory markers and carotid plaques. Longitudinal studies are needed to confirm these associations and elucidate the temporal relationship between inflammation, renal function, and atherosclerosis. Second, the study population was limited to patients admitted to a single nephrology division, which may limit the generalizability of the findings to broader CKD populations. Third, the reliance on ultrasound imaging for carotid plaque assessment, while widely used, may be subject to operator variability and measurement error. Fourth, the absence of inflammatory markers such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) may overlook potential inflammatory pathways involved in the development of carotid plaques, thus limiting a comprehensive understanding of the underlying mechanisms. Fifth, the relatively small sample size may affect the generalizability of the findings. Therefore, further studies with larger cohorts are required to validate our results and confirm the observed associations. Additionally, other factors such as genetic predisposition and the impact of concurrent medications were not accounted for in our analysis, which could confound the observed associations. Last limitation is the potential bias introduced by focusing on hospitalized CKD patients. Due to the highly individualized nature of hospitalization processes—such as patients admitted for various reasons including diagnostic procedures, treatment adjustments, or preparation for dialysis—the underlying conditions for admission could vary significantly and are difficult to categorize uniformly. This heterogeneity in hospitalization reasons may influence the associations observed in our study, and therefore, caution is needed when generalizing the results to broader CKD populations.

Conclusion

In conclusion, our study demonstrated that elevated levels of inflammatory markers were significantly associated with the presence of carotid plaques in CKD patients, with eGFR partially mediating this relationship. These findings highlighted the critical role of inflammation in the pathogenesis of atherosclerosis in CKD patients and underscore the importance of maintaining optimal renal function to mitigate atherosclerosis risk.

Table 3 Mediation of eGFR for the associations between inflammatory biomarkers and carotid plaque

Independent variable	Mediator	Total effect		Indirect effect		Direct effect		Proportion mediated, % (95% CI)
		Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	Coefficient (95% CI)	*P*	
LnSIRI	eGFR	0.133 (0.062, 0.212)	< 0.001	0.020 (0.007, 0.036)	0.004	0.113 (0.045, 0.194)	0.004	14.8 (5.1, 32.1)
LnSII	eGFR	0.021 (0.002, 0.029)	0.008	0.004 (0.000, 0.016)	0.016	0.018 (0.000, 0.025)	0.048	17.5 (2.2, 83.8)
LnAISI	eGFR	0.027 (0.009, 0.035)	< 0.001	0.002 (-0.001, 0.006)	0.204	0.026 (0.009, 0.033)	< 0.001	5.7 (-4.4, 19.4)
LnMHR	eGFR	0.055 (0.011, 0.073)	0.004	0.008 (0.001, 0.023)	< 0.001	0.047 (0.009, 0.062)	0.008	15.1 (3.9, 41.7)
LnNHR	eGFR	0.077 (-0.003, 0.124)	0.076	0.033 (0.011, 0.055)	< 0.001	0.043 (-0.034, 0.103)	0.344	43.4 (-191.6, 335.6)
LnMLR	eGFR	0.180 (0.135, 0.195)	< 0.001	0.026 (0.005, 0.053)	0.008	0.154 (0.101, 0.179)	< 0.001	14.7 (3.1, 32.5)
LnNLR	eGFR	0.133 (0.062, 0.212)	0.100	-0.019 (-0.043, 0.001)	0.056	0.078 (0.009, 0.148)	0.012	-31.6 (-308.9, 200.7)

AISI: aggregate inflammatory status index; CI: confidence interval; eGFR: estimated glomerular filtration rate; Ln: natural logarithm; MHR: monocyte to high-density lipoprotein cholesterol ratio; MLR: monocyte to lymphocyte ratio; NHR: neutrophil to high-density lipoprotein cholesterol ratio; NLR: neutrophil to lymphocyte ratio; SII: systemic immune-inflammation index; SIRI: systemic inflammatory response index

Abbreviations

CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
SIRI	systemic inflammatory response index
SII	systemic immune-inflammation index
AISI	aggregate inflammatory status index
MHR	monocyte to high-density lipoprotein cholesterol ratio
NHR	neutrophil to high-density lipoprotein cholesterol ratio
MLR	monocyte to lymphocyte ratio
BMI	body mass index
IMT	intima-media thickness
RCS	restricted cubic spline
KDIGO	Kidney Disease: Improving Global Outcomes
CCVD	cardiovascular and cerebrovascular diseases
OR	odds ratio
CI	confidence interval
ALT	alanine aminotransferase
AST	aspartate aminotransferase
TNF-α	tumor necrosis factor-alpha
IL-6	interleukin-6
BUN	blood urea nitrogen
SCr	serum creatinine
HDL-C	high-density lipoprotein cholesterol
IQR	interquartile range
NLPR	neutrophil-to-lymphocyte platelet ratio

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03826-1.

Supplementary Material 1

Author contributions

WJ, XD and YF designed and directed the study, LW, JW, FX, LZ, XJ and JJ participated in data collection and maintenance, LW, JW, LZ and XJ analyzed the data, WJ, LW and JJ interpreted the results and writing. WJ, XD and YF participated in reviewing the manuscript, the maintenance of dataset and facilitating the acquisition of data. All authors read and approved the final manuscript.

Funding

This work was supported by Shanghai Federation of Nephrology Project supported by Shanghai ShenKang Hospital Development Center, No. SHDC2202230; Shanghai Clinical Research Center for Kidney Disease, No. 22MC1940100; Shanghai Municipal Key Clinical Specialty (shslczdzk02501); Shanghai Key laboratory of Kidney and Blood Purification (14DZ226022, 20DZ2271600); National Nature Science Foundation of China, No. 82102289.

Data availability

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the ethical board from Zhongshan Hospital, Fudan University (Approval Number B2021–740). All eligible participants provided written informed consent. The study was conducted in accordance with the Helsinki Declaration (WMA Declaration of Helsinki, 2013).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Nephrology, Zhongshan Hospital, Fudan University, No 180 Fenglin Rd., Shanghai, China
[2]Shanghai Clinical Research Center for Kidney Disease, Shanghai, China
[3]Shanghai Institute of Kidney and Dialysis, Shanghai, China

Received: 1 August 2024 / Accepted: 16 October 2024
Published online: 22 October 2024

References

1. De Nicola L, Minutolo R. Worldwide growing epidemic of CKD: fact or fiction? Kidney Int. 2016;90(3):482–4.
2. Arroyo D, Betriu A, Martinez-Alonso M, Vidal T, Valdivielso JM, Fernandez E. Investigators from the ns: observational multicenter study to evaluate the prevalence and prognosis of subclinical atheromatosis in a Spanish chronic kidney disease cohort: baseline data from the NEFRONA study. BMC Nephrol. 2014;15:168.
3. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. N Engl J Med. 1999;340(1):14–22.
4. Roumeliotis A, Roumeliotis S, Panagoutsos S, Theodoridis M, Argyriou C, Tavridou A, Georgiadis GS. Carotid intima-media thickness is an independent predictor of all-cause mortality and cardiovascular morbidity in patients with diabetes mellitus type 2 and chronic kidney disease. Ren Fail. 2019;41(1):131–8.
5. Szeto CC, Chow KM, Woo KS, Chook P, Ching-Ha Kwan B, Leung CB, Kam-Tao Li P. Carotid intima media thickness predicts cardiovascular diseases in Chinese predialysis patients with chronic kidney disease. J Am Soc Nephrol. 2007;18(6):1966–72.

6. Mihai S, Codrici E, Popescu ID, Enciu AM, Albulescu L, Necula LG, Mambet C, Anton G, Tanase C. Inflammation-Related Mechanisms in Chronic Kidney Disease Prediction, Progression, and Outcome. *J Immunol Res* 2018, 2018:2180373.
7. Silverstein DM. Inflammation in chronic kidney disease: role in the progression of renal and cardiovascular disease. Pediatr Nephrol. 2009;24(8):1445–52.
8. Tang L, Deng Y, Lai J, Guo X, Liu P, Li S, Liu X. Predictive effect of system inflammation response index for progression of chronic kidney disease in Non-dialyzing Patient. J Inflamm Res. 2023;16:5273–85.
9. Guo W, Song Y, Sun Y, Du H, Cai Y, You Q, Fu H, Shao L. Systemic immune-inflammation index is associated with diabetic kidney disease in type 2 diabetes mellitus patients: evidence from NHANES 2011–2018. Front Endocrinol (Lausanne). 2022;13:1071465.
10. Goikuria H, Vandenbroeck K, Alloza I. Inflammation in human carotid atheroma plaques. Cytokine Growth Factor Rev. 2018;39:62–70.
11. Mury P, Chirico EN, Mura M, Millon A, Canet-Soulas E, Pialoux V. Oxidative stress and inflammation, key targets of atherosclerotic plaque progression and vulnerability: potential impact of physical activity. Sports Med. 2018;48(12):2725–41.
12. Stam F, van Guldener C, Schalkwijk CG, ter Wee PM, Donker AJ, Stehouwer CD. Impaired renal function is associated with markers of endothelial dysfunction and increased inflammatory activity. Nephrol Dial Transpl. 2003;18(5):892–8.
13. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, De Zeeuw D, Hostetter TH, Lameire N, Eknoyan G. Definition and classification of chronic kidney disease: a position statement from kidney disease: improving global outcomes (KDIGO). Kidney Int. 2005;67(6):2089–100.
14. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
15. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, Csiba L, Desvarieux M, Ebrahim S, Fatar M et al. Mannheim carotid intima-media thickness consensus (2004–2006). An update on behalf of the Advisory Board of the 3rd and 4th Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis* 2007, 23(1):75–80.
16. Stoll G, Bendszus M. Inflammation and atherosclerosis: novel insights into plaque formation and destabilization. Stroke. 2006;37(7):1923–32.
17. Zhang L, Lyu Q, Zhou W, Li X, Ni Q, Jiang S, Shi G. High systemic immune-inflammation index is associated with carotid plaque vulnerability: new findings based on carotid ultrasound imaging in patients with acute ischemic stroke. Front Neurol. 2022;13:959531.
18. Liao M, Liu L, Bai L, Wang R, Liu Y, Zhang L, Han J, Li Y, Qi B. Correlation between novel inflammatory markers and carotid atherosclerosis: a retrospective case-control study. PLoS ONE. 2024;19(5):e0303869.
19. Chen JW, Li C, Liu ZH, Shen Y, Ding FH, Shu XY, Zhang RY, Shen WF, Lu L, Wang XQ. The role of monocyte to High-Density Lipoprotein Cholesterol Ratio in prediction of Carotid Intima-Media thickness in patients with type 2 diabetes. Front Endocrinol (Lausanne). 2019;10:191.
20. Glorieux G, Gryp T, Perna A. Gut-derived metabolites and their role in Immune Dysfunction in chronic kidney disease. Toxins (Basel) 2020, 12(4).
21. Gistera A, Hansson GK. The immunology of atherosclerosis. Nat Rev Nephrol. 2017;13(6):368–80.
22. Jankowski J, Floege J, Fliser D, Bohm M, Marx N. Cardiovascular Disease in chronic kidney disease: pathophysiological insights and therapeutic options. Circulation. 2021;143(11):1157–72.
23. Libby P. Inflammation during the life cycle of the atherosclerotic plaque. Cardiovasc Res. 2021;117(13):2525–36.
24. Schieffer B, Selle T, Hilfiker A, Hilfiker-Kleiner D, Grote K, Tietge UJ, Trautwein C, Luchtefeld M, Schmittkamp C, Heeneman S, et al. Impact of interleukin-6 on plaque development and morphology in experimental atherosclerosis. Circulation. 2004;110(22):3493–500.

Publisher's note